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SUBMISSION OF PRIORITY DOCUMENT

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Sir:

Pursuant to rule 55(b) of the Rules of Practice in Patent Cases, Applicant(s) is/are submitting herewith a certified copy of the European Application No. 00311407.1 filed December 19, 2000, upon which the claim for priority under 35 U.S.C. § 119 was made in the United States.

It is respectfully requested that the priority document be made part of the file history.

Respectfully submitted,

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Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

00311407.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Page 2 de l'attestation

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STABILIZATION OF ANTIBODIES OR FRAGMENTS THEREOF

TECHNICAL FIELD

The present invention generally relates to the stabilisation of antibodies, or fragments derived thereof, in detergent compositions, in particular in bleaching detergent compositions.

BACKGROUND AND PRIOR ART

Antibodies are polypeptides which are capable of binding specifically to compounds against which they were raised. Antibodies are used for a variety of purposes, such as immuno assays. More recently, their application in detergent and cleaning applications has been proposed. WO-A-98/56885 (Unilever) discloses a bleaching enzyme which is capable of generating a bleaching chemical and having a high binding affinity for stains present on fabrics, as well as an enzymatic bleaching composition comprising said bleaching enzyme, and a process for bleaching stains on fabrics. The binding affinity may be formed by a part of the polypeptide chain of the bleaching enzyme, or the enzyme may comprise an enzyme part which is capable of generating a bleach chemical that is coupled to a reagent having the high binding affinity for stains present on fabrics. In the latter case, the reagent may be bi-specific, comprising one specificity for stain and one for enzyme. Examples of such bi-specific reagents mentioned in the disclosure are antibodies, especially those derived from *Camelidae* having only a variable region of the heavy chain polypeptide (V_{HH}), peptides, peptidomimics, and other organic molecules. The enzyme usually is an oxidase, such as glucose oxidase, galactose oxidase and alcohol oxidase, which is capable of forming hydrogen peroxide or another bleaching agent. Thus,

if the multi-specific reagent is an antibody, the enzyme forms an enzyme/antibody conjugate which constitutes one ingredient of a detergent composition. During washing, said enzyme/antibody conjugate of the detergent composition is targeted to stains on the clothes by another functional site of the antibody, while the conjugated enzyme catalyses the formation of a bleaching agent in the proximity of the stain and the stain will be subjected to bleaching.

Little attention has been paid so far to the manner in which such antibodies are added to the detergent composition in order to achieve the desired bleaching effect of the enzyme-antibody complex. It was found that the storage stability of the antibodies in such cleaning compositions problem is not always satisfactory. Extensive prior art exists regarding the granulation of enzymes for use in detergents, but this technology cannot be directly transferred to antibodies.

The purpose of the present invention is to provide a method by which antibodies can be incorporated into (bleaching) detergent compositions in a stable manner.

It has now surprisingly been found that it is possible to incorporate antibodies into detergent compositions in a stable manner if the antibodies are granulated with simple salts, such as sodium or potassium salts. This is the converse to granulation of enzymes, whereby complicated measures have to be taken in the granulation technology in order to provide the required stability and the lifetime of the enzyme.

Moreover, it was surprisingly found the antibody activity was improved when they were stored in the granulated form, as compared to common protein storage methods. This therefore imparts a substantially improved lifetime of the antibody and its associated performance in a powdered form or product form.

DEFINITION OF THE INVENTION

According to a first aspect of the invention, there is provided an antibody granule consisting essentially of one or more antibodies, or fragments derived thereof, granulated with an alkali metal salt.

According to a second aspect, there is provided an enzymatic stain bleaching or anti dye-transfer composition comprising the antibody granule.

DESCRIPTION OF THE INVENTION

In a first aspect, the invention relates to an antibody granule consisting essentially of one or more antibodies, or fragments derived thereof, granulated with an alkali metal salt. As stated above, antibodies are polypeptides which are capable of binding specifically to compounds against which they were raised. For the purpose of this invention, "antibodies" also includes fusion proteins of antibodies with enzymes, such as disclosed in WO-A-98/56885. "antibodies" also includes other polypeptides which have a high binding affinity for specific other molecules or structures, for instance cellulose binding domains (CBD's) which occur in cellulases.

The degree of binding of a compound A to another molecule B can be generally expressed by the chemical equilibrium constant K_d resulting form the following binding reaction:

$$[A]+[B] \rightharpoonup [A::B]$$

The chemical equilibrium constant K_d is then given by:

$$K_d = \frac{[A] \times [B]}{[A::B]}$$

Whether the binding to the substance is specific or not can be judged from the difference between the binding (K_d value) of the compound to that substance, versus the binding to the material to which that substance is applied, or versus other substances one does not want to oxidise. For substances which occur in stains, the latter material can be envisioned to be the fabric on which the stain is present, or the dye molecules on coloured garments. The difference between the two binding constants should be minimally 100, and preferably more that 1000. Typically, the compound should bind the coloured substance with a K_d value of $1*10^{-4}$ to $1*10^{-6}$, with a background binding to fabric with a K_d of $1*10^{-7}$ to $1*10^{-3}$. Higher binding affinities (K_d of less than $1*10^{-5}$) and/or a larger difference between coloured substance and background binding would increase the selectivity of the oxidation process. Also, the weight efficiency of the compound in the total detergent composition would be increased and smaller amounts of the compound would be required.

Antibodies can be derived from several sources. From mice, monoclonal antibodies can be obtained which possess very high binding affinities. From such antibodies, Fab, Fv or scFv fragments, can be prepared which have retained their binding properties. Such antibodies or fragments can be produced through recombinant DNA technology by microbial fermentation. Well known production hosts for antibodies and their fragments are yeast, moulds or bacteria.

A class of antibodies of particular interest is formed by the Heavy Chain antibodies as found in Camelidae, like the camel or the llama. The binding domains of these antibodies consist of a single polypeptide fragment, namely the variable region of the heavy chain polypeptide (HC-V). In contrast, in the classic antibodies (murine, human, etc.), the binding domain consist of two polypeptide chains (the variable regions of the heavy chain (V_h) and the light

chain (V_H)). Procedures to obtain heavy chain immunoglobulins from Camelidae, or (functionalized) fragments thereof, have been described in WO-A-94/04678 (Casterman and Hamers) and WO-A-94/25591 (Unilever and Free University of Brussels).

Alternatively, binding domains can be obtained from the V_H fragments of classical antibodies by a procedure termed "camelization". Hereby the classical V_H fragment is transformed, by substitution of a number of amino acids, into a HC-V-like fragment, whereby its binding properties are retained. This procedure has been described by Riechmann et al. in a number of publications (J. Mol. Biol. (1996) **259**, 957-969; Protein. Eng. (1996) **9**, 531-537, Bio/Technology (1995) **13**, 475-479). Also HC-V fragments can be produced through recombinant DNA technology in a number of microbial hosts (bacterial, yeast, mould), as described in WO-A-94/29457 (Unilever).

Methods for producing fusion proteins that comprise an enzyme and an antibody or that comprise an enzyme and an antibody fragment are already known in the art. One approach is described by Neuberger and Rabbits (EP-A-194 276). A method for producing a fusion protein comprising an enzyme and an antibody fragment that was derived from an antibody originating in *Camelidae* is described in WO-A-94/25591. A method for producing bi-specific antibody fragments is described by Holliger et al. (1993) PNAS **90**, 6444-6448.

A particularly attractive feature of antibody binding behaviour is their reported ability to bind to a "family" of structurally-related molecules. For example, in Gani et al. (J. Steroid Biochem. Molec. Biol. **48**, 277-282) an antibody is described that was raised against progesterone but also binds to the structurally-related steroids, pregnanedione, pregnanolone and 6-hydroxy-progesterone. Therefore, using the same approach, antibodies

could be isolated that bind to a whole "family" of stain chromophores (such as the polyphenols, porphyrins, or caretenoids as described below). A broad action antibody such as this could be used to treat several different stains when coupled to a bleaching enzyme.

Several classes of other compounds can be envisaged which deliver the specific binding capability. In the following we will give a number of examples of such other compounds having such binding capabilities, without pretending to be exhaustive.

1. Peptides.

Peptides usually have lower binding affinities to the substances of interest than antibodies. Nevertheless, the binding properties of peptides can be sufficient to deliver the desired binding effect. A peptide which is capable of binding selectively to another substance can for instance be obtained from a protein which is known to bind to that specific substance. An example of such a peptide would be a binding region extracted from an antibody raised against that substance.

Alternatively, peptides which bind to such substance can be obtained by the use of peptide combinatorial libraries. Such a library may contain up to 10^{10} peptides, from which the peptide with the desired binding properties can be isolated. (R.A. Houghten, Trends in Genetics, Vol 9, no &, 235-239). Several embodiments have been described for this procedure (J. Scott et al., Science (1990), Vol. 249, 386-390; Fodor et al., Science (1991), Vol. 251, 767-773; K. Lam et al., Nature (1991) Vol. 354, 82-84; R.A. Houghten et al., Nature (1991) Vol. 354, 84-86).

Suitable peptides can be produced by organic synthesis, using for example the Merrifield procedure (Merrifield, J.Am.Chem.Soc. (1963), 85, 2149-2154). Alternatively, the peptides can be produced by recombinant DNA technology in microbial hosts (yeast, moulds,

bacteria)(K.N. Faber et al., Appl. Microbiol. Biotechnol. (1996) 45, 72-79).

2. Pepidomimics. In order to improve the stability and/or binding properties of a peptide, the molecule can be modified by the incorporation of non-natural amino acids and/or non-natural chemical linkages between the amino acids. Such molecules are called peptidomimics (H.U. Saragovi et al. Bio/Technology (1992), Vol 10, 773-778; S. Chen et al., Proc.Natl.Acad. Sci. USA (1992) Vol 89, 5872-5876). The production of such compounds is restricted to chemical synthesis.

3. Other organic molecules.

It can be readily envisaged that other molecular structures, which need not be related to proteins, peptides or derivatives thereof, can be found which bind selectively to substances. For example, certain polymeric RNA molecules which have been shown to bind small synthetic dye molecules (A. Ellington et al., Nature (1990) vol. 346, 818-822). Such binding compounds can be obtained by the combinatorial approach, as described for peptides (L.B. McGown et al., Analytical Chemistry, november 1, 1995, 663A-668A).

This approach can also be applied for purely organic compounds which are not polymeric. Combinatorial procedures for synthesis and selection for the desired binding properties have been described for such compounds (Weber et al., Angew.Chem.Int.Ed.Engl. (1995), 34, 2280-2282; G. Lowe, Chemical Society Reviews (1995) Vol 24, 309-317; L.A. Thompson et al. Chem. Rev. (1996), Vol. 96, 550-600). Once suitable binding compounds have been identified, they can be produced on a larger scale by means of organic synthesis.

When using the approach disclosed in WO-A-98/56885 (Unilever), the antibodies are directed at stains present on fabrics. Several classes of substances one would like to

oxidise can be envisaged: For detergents applications, coloured or non-coloured substances which may occur as stains on fabrics can be a target. Several types or classes of coloured substances which may occur in stains can be envisaged:

1. Porphyrin derived structures.

Porphyrin structures, often coordinated to a metal, form one class of coloured substances which occur in stains. Examples are heme or haematin in blood stain, chlorophyll as the green substance in plants, e.g. grass or spinach. Another example of a metal-free substance is bilirubin, a yellow breakdown product of heme.

2. Tannins, polyphenols

Tannins are polymerised forms of certain classes of polyphenols. Such polyphenols are catechins, leuantocyanins, etc. (P. Ribéreau-Gayon, Plant Phenolics, Ed. Oliver & Boyd, Edinburgh, 1972, pp.169-198). These substances can be conjugated with simple phenols like e.g. gallic acids. These polyphenolic substances occur in tea stains, wine stains, banana stains, peach stains, etc. and are notoriously difficult to remove.

3. Carotenoids.

(G.E. Bartley et al., The Plant Cell (1995), Vol 7, 1027-1038). Carotenoids are the coloured substances which occur in tomato (lycopene, red), mango (β-carotene, orange-yellow). They occur in food stains (tomato) which are also notoriously difficult to remove, especially on coloured fabrics, when the use of chemical bleaching agents is not advised.

4. Anthocyanins.

(P. Ribéreau-Gayon, Plant Phenolics, Ed. Oliver & Boyd, Edinburgh, 1972, 135-169). These substance are the highly coloured molecules which occur in many fruits and flowers. Typical examples, relevant for stains, are berries, but also wine. Anthocyanins have a high diversity in glycosidation patterns.

5. Maillard reaction products

Upon heating of mixtures of carbohydrate molecules in the presence of protein/peptide structures, a typical yellow/brown coloured substance arises. These substances occur for example in cooking oil and are difficult to remove from fabrics.

6. Dyes in solution.

For the prevention of dye transfer from a coloured piece of fabric to other garments during the wash, it valuable to specifically bleach the dye molecules in the wash solution. Several types of fabric dyes are used, and can therefore be envisaged to be a target for the oxidation process: e.g. sulphur dyes, vat dyes, direct dye, reactive dyes and azoic dyes..

The antibody of the invention granule contains an alkali metal salt, preferably a sodium salt. The preferred salt is sodium sulphate. The granules are manufactured using standard granulation technology, e.g. by mixing the ingredients in a mixing apparatus, preferably in the presence of a binder.

(a) The enzyme

The antibody granules according to the invention may be used in a bleaching detergent composition. Such enzymatic detergent compositions comprise an oxidising or bleaching enzyme. The enzyme may either be an enzyme exhibiting peroxidase activity (which is then used together

with a source of hydrogen peroxyde), or an enzyme exhibiting oxidase activity on phenolic compounds, such as phenol oxidase or laccase. Suitable enzymes are disclosed in EP-A-495 835 (Novo Nordisk). For instance, suitable peroxidases may be isolated from and are producible by plants or micro-organisms such as bacteria or fungi. Preferred fungi are strains belonging to the class of the Basidiomycetes, in particular Coprinus, or to the class of Hyphomycetes, in particular Arthromyces, especially Arthromyces ramosus. Other preferred sources are Hormographiella sp., Myxococcus sp., Corallococcus sp. (WO-A-95/11964), or Soybean peroxidase. Examples of suitable enzymes exhibiting oxidase activity on phenolic compounds are catechol oxidase and laccase and bilirubin oxidase. The laccase can be derived from fungi such as Trametes sp., Collybio sp., Fomes sp., Lentinus sp., Pleurotus sp., Rhizoctonia sp., Aspergillus sp., Neurospora sp., Podospora sp., Phlebia sp., Coriolus sp., Myceliophthora sp., Coprinus sp., Panaeolus sp., Psathyrella sp. (WO-A-96/06930). Bilirubin oxidase can be obtained from Myrothecium sp. or Stachibotrys sp.

The enzymatic oxidation compositions of the invention comprise about 0.001 to 10 milligrams of active enzyme per litre. A detergent composition will comprise about 0.001% to 1% of active enzyme (w/w). The enzyme activity can be expressed as ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)units. One ABTS unit represents the amount of enzyme which oxidizes ABTS, resulting in an increase of 1 optical density at 418 nm in one minute. Conditions for the activity assay are 2 mM ABTS, 1 mM H_2O_2, 20 mM Tris, pH 9. The enzyme activity which is added to the enzymatic oxidation composition will be about 10 to 10^6 ABTS units per litre, preferably 10^3 to 10^5 ABTS units per litre.

The oxidising enzymes can usefully be added to the detergent composition in any suitable form, i.e. the form of a granular composition, a liquid or a slurry of the enzyme,

or with carrier material (e.g. as in EP-A-258 068 and the Savinase (TM) and Lipolase (TM) products of Novo Nordisk). A good way of adding the enzyme to a liquid detergent product is in the form of a slurry containing 0.5 to 50 % by weight of the enzyme in a ethoxylated alcohol nonionic surfactant, such as described in EP-A-450 702 (Unilever).

(b) The source of hydrogen peroxide

Another ingredient of the enzymatic bleach or anti dye-transfer compositions according to the invention is a source of hydrogen peroxide. This may be hydrogen peroxide itself, but more stabilized forms of hydrogen peroxide such as perborate or percarbonate are preferred. Especially preferred is sodium percarbonate.

Alternatively, one may employ an enzymatic hydrogen peroxide-generating system. The enzymatic hydrogen peroxide-generating system may in principle be chosen from the various enzymatic hydrogen peroxide-generating systems which have been disclosed in the art. For example, one may use an amine oxidase and an amine, an amino acid oxidase and an amino acid, cholesterol oxidase and cholesterol, uric acid oxidase and uric acid, or xanthine oxidase with xanthine. Preferably, however, the combination of a C_1-C_4 alkanol oxidase and a C_1-C_4 alkanol is used, and especially preferred is the combination of methanol oxidase and ethanol. The methanol oxidase is preferably isolated from a catalase-negative Hansenula polymorpha strain. (see for example EP-A-244 920 (Unilever)).

The invention will now be further illustrated in the following, non-limiting Examples.

Example 1

A Bi-head antibody (1249) was constructed (anti Glucose Oxidase - anti polyphenols /Red wine (Côtes du Rhône

wine (Co-op, U.K.)) according to the method described in WO-A-99/23221 (Unilever). Granules were prepared with the lyophilised antibody 1249 to investigate the storage properties conferred by using different materials. The Bi-head (containing Bicine and NaCl from Ion exchange purification process) was combined with Na_2SO_4. The mixture was then thoroughly mixed and lightly ground in a pestle and mortar. 2.23g of a solution of CP5 acrylate-maleate copolymer (40% by weight) was then added drop-wise to the solid mixture with frequent mixing. (The 2.23g was enough to cause the solids to "granulate" on mixing. The resultant granules were then transferred to a flat tray and left to dry in flowing air at room temperature. The granules lost 4.5% by weight on drying. The dry granules were then milled to less than 1000 micron.

Granule composition:

Material	wt%	% by weight
bi-head	0.4	1.9
NaCl/bicene	1.227	5.9
Na2SO4	18.453	88.0
CP5 coplymer dry basis)	0.892	4.3

In addition to the above, granules were made with glucose instead of Na_2SO_4 or where 50% of the Na_2SO_4 was replaced with glucose.

Storage Trial

This was set up in fully formulated OMO MA powder, which was dispensed in amounts of 1g /glass vial. Granules were dosed in at 50 milligram per vial. This was calculated to give approximately 1 mg/ml of bi-head when the contents of a vial were dissolved in 500 ml water. Labelled vials were placed in humidity chambers, for samples stored at room temperature (20°C± 2) the chamber contained a saturated solution of

Potassium carbonate to provide about 44% humidity. For the samples stored at 37°C ±1, a saturated solution of NaCl was used to give about 75% humidity. Samples were removed at regular intervals and assayed for bi-specfic activity.

Assay for Bi-specific activity

Microtitre (Nunc Maxisorb plates were sensitised over night at 37°C with 200µl/well of red wine (Co-op Cote Du Rhone). Six vials were removed from each humidity chamber [2 of each granule type] and the contents of each vial were added to 500ml of de-mineralised water. For a control, fresh granules were weighed out and added to 1g of OMO MA, each was added to separate flasks containing 500 ml of de-mineralised water. The contents of each flask were stirred for 5 minutes before a 250µl aliquot was removed from each and diluted in PBST pH 7.4 to give 250 ng/ml bi-head.

Control and sample dilutions were dispensed at 200µl per well in duplicate into the wells of washed red wine plates. An incubation of 30 minutes/room temp. followed before the unbound samples were removed by three washes in PBST. Glucose oxidase (Gox) at 25µg ml in PBST was dispensed to all wells containing sample and to additional wells that had previously been incubated only with PBST; this was to check for non-specific binding of the enzyme to the sensitised plate. Incubation was carried out for 1 hour; unbound Gox was removed by washing with PBST. Substrate containing TMB, 10mM Glucose and 2µg/ml HRP was dispensed to each well and allowed to develop for 20 minutes before the reaction was stopped by the addition of 100µl/well of 1M HCl. Plates were read using a Dynatech plate reader at 450nm.

Duplicate readings from each dilution were averaged and plotted as a percentage of the appropriate control. The results are shown in Figures 1 and 2. They can be summarized as follows:

Room temperature samples

Granules containing sodium sulphate showed between 100 and 170% activity of that seen in the control samples. The glucose granules showed variability with one sample having 100% activity and other 80% activity. In subsequent assays a higher level of activity than the control sample was seen up until day 33. All granules tested showed a fall in activity to between 50 and 80% of the control.

Samples at 37°C

All samples showed over 100% activity of the control samples. By day 7, the bihead granulated with Sodium Sulphate still showed binding levels above the control granules. The remaining samples showed a significant decrease in the bi-specific activity when compared to the appropriate controls. At assay on day 15, no activity was detected in any of the stored samples.

The storage conditions chosen were very different and the results obtained reflect this; at room temperature activity levels are still above 55% after 33 days. At 37°C there is a dramatic drop off in activity between days 7 and 15. The effect of the ingredients following storage are variable, at 37°C/77%H, whereby the presence of glucose had a significant adverse affect on antibody activity (these granules showed a reduction in activity of up to 60%). The granules containing both sodium sulphate and glucose showed a similar trend. However good activity was still detected on day 7 in the sodium sulphate granules and the same granules stored at room temp/40%H had high antibody activity.

(1) The granulation process with a simple salt did not detrimentally affect the activity of the bi-head.

(2) Storage of antibodies in a granulated form have a superior antibody activity as compared to conventional protein storage methods.

CLAIMS

1. Antibody granule consisting essentially of one or more antibodies, or fragments derived thereof, granulated with an alkali metal salt.

2. Antibody granule according to claim 1, wherein the alkali metal is sodium or potassium.

3. Antibody granule according to any one of the preceding claims, wherein the granule consists for more than 80%, preferably more than 90% of the alkali metal salt.

4. Antibody granule according to claim 3, further comprising a polymeric binder such as a acrylate-maleate copolymer.

5. Antibody granule according to any one of the preceding claims, wherein the antibody has a chemical equilibrium constant K_d for its antigen of less than $1*10^{-4}$, preferably less than $1*10^{-6}$.

6. Antibody granule according to any one of the preceding claims, wherein the chemical equilibrium constant K_d for the antigen is less than $1*10^{-7}$.

7. A detergent composition comprising the antibody granule of any one of the preceding claims.

8. An enzymatic stain bleaching composition comprising the antibody granule of claims 1-7.

9. An enzymatic anti dye-transfer composition comprising the antibody granule of claims 1-7.

10. Process for preparing an antibody granule according to claims 1-7, in which the antibody is granulated with an alkali metal salt.

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ABSTRACT

There is provided an antibody granule, consisting essentially of one or more antibodies, or fragments derived thereof, granulated with an alkali metal salt.

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Figure 1 - Storage at room temperature

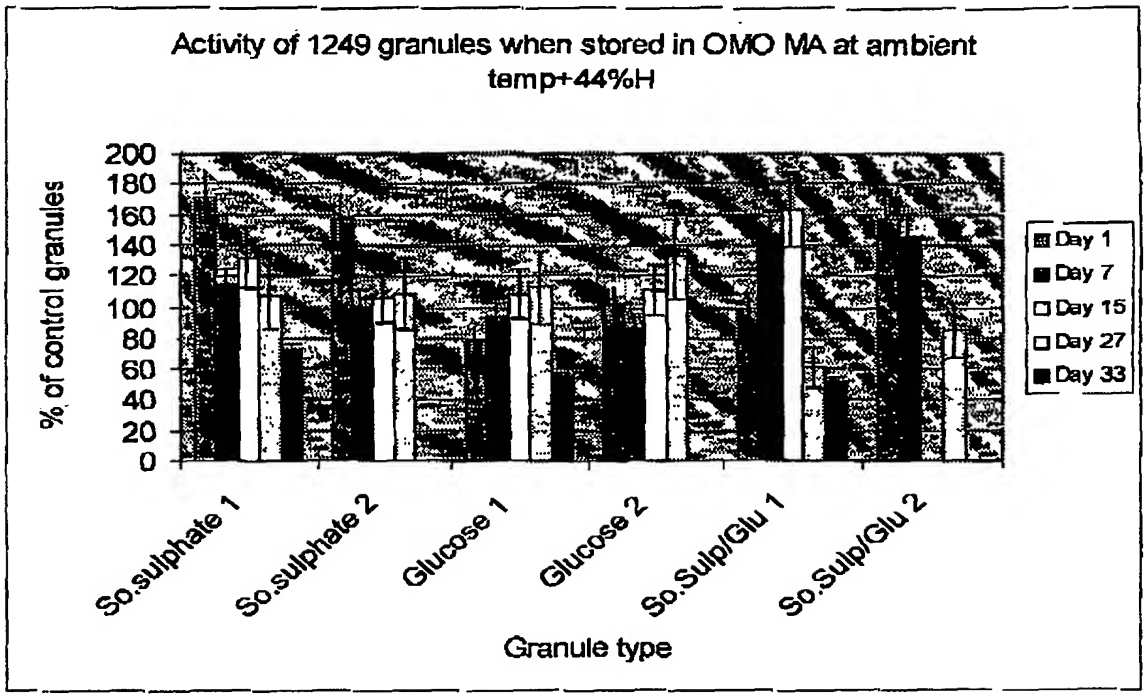

Figure 2 - storage at 37°C